IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Werner LUBITZ et al

Serial Number: 09/147,693

Filed: February 17, 1999

Group Art Unit: 1636

Examiner: Sandals, W.

8/C
6/3/00

For: NEW SYSTEMS FOR THE REGULATION OF GENE EXPRESSION

RESPONSE UNDER 37 C.F.R. §1.111

Commissioner for Patents
Washington, D.C. 20231

May 31, 2000

Sir:

In response to the Office Action dated March 2, 2000, please amend the application as follows.

IN THE CLAIMS:

Claim 46, line 3, before "repressor" insert --cI--.

REMARKS

The Office Action dated March 2, 2000 has been received and carefully noted. The above amendments and the following remarks are submitted as a full and complete response thereto.

Claims 63-65, 71 and 72 were rejected under 35 USC §112, first paragraph as lacking enablement regarding how to make and use a bacterial live cell or a ghost cell as a vaccine. The Office Action indicates that the present application does not set forth the protein required for vaccination. The Office Action implies that a specific protein must be identified which elicits

the production of protective antibodies. Applicants respectfully point out that a live bacteria and a ghost cell would have the same surface antigens as the infectious bacteria and thus the same immunogenic properties would be expected. Applicant's response of January 18, 2000 submitted references which show that ghost bacterial cells are known in the art to be useful as vaccines. The present application discusses the preparation of the ghosts on page 9. As discussed on page 9, ghosts can be prepared by the stringently controlled expression of the E-lysis gene from PhiX174 whose expression product forms a tunnel through the bacterial cell wall coat which causes the cell contents to pour out. This lethal gene can be regulated by the mutated operator sequences according to the present invention. The use of the mutated operator sequences allows the bacteria to be cultured at a temperature near the body temperature of the animal to receive the vaccine which should result in surface proteins which are the same as the surface proteins of the infectious bacteria. Regarding live bacterial cells, the mutated operator sequences can be used as a safety cassette such that the inoculated bacteria are killed when fever is induced. As is clear from the above discussion, the present claims are not directed to a specific recombinant protein to be expressed on the surface of the host cell. Since the claims are not directed to a specific protein and the live bacterial cells and ghost cells would have all of the same surface antigens as the infectious bacteria, applicants contend that identification of a specific protein on the

surface of the cells is not necessary to provide enablement for the present claims. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 38-42, 44-48, 50, 52-62, 66-70 and 73-76 were rejected under 35 USC §103(a) as unpatentable over Eliason, in view of Pakula, Benson and Zacharias. As pointed out in applicant's prior response, Eliason discloses mutated O_R or O_L DNA sequences exhibiting a different repressor binding affinity compared to the wild type sequence. Eliason does not contain any indication regarding the existence of mutated operator sequences leading to an increased thermostability of the repressor binding affinity. Pakula discloses mutants of the λ Cro protein which is a product of the transcript starting from the promotor P_R and binds to the λ DNA in the region of the operator O_R. This way transcription is blocked by the adjacent promotor P_{RM}. The λ Cro protein is different from the λ repressor protein cI discussed in the present application. Benson describes the production of mutated λ operator sequences for analyzing the binding of wild-type repressors. One of the operator sequences produced by Benson shows a higher affinity for the λ wild-type repressor than the wild-type operator sequence (superoperator). Benson does not suggest or disclose that the thermostability of the binding affinity of a temperature sensitive λ cI repressor can be increased by mutations in the λ operator sequence. Zacharias discloses the production of a mutated λ operator sequence which does not have a higher λ repressor

binding affinity than the wild type sequence. Zacharias does not suggest or disclose increased thermostability regarding the binding affinity of a temperature sensitive λ repressor. Zacharias states that mutations of bases can have severe effects on binding and suggests that his approach could be used to locally readjust conformations by introducing small structural alterations. Applicants were unable to find any disclosure in Zacharias which discusses sequence changes which result in increased thermostability. Applicants point out that the Cro protein described in Pakula is different from the λ repressor cI and that none of the cited prior art individually or in combination suggests or discloses the existence of operator mutations which lead to an improvement in the thermostability of the binding affinity of a temperature sensitive λ repressor. In view of the above discussion, applicants request that this rejection be withdrawn.

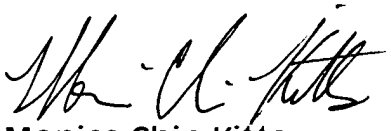
Claim 51 was rejected under 35 USC §103(a) as unpatentable over Eliason, in view of Pakula, Benson and Zacharias further in view of Vasquez. Vasquez was cited for the disclosure of a lambda operator sequence in operative linkage with a suicide gene. Vasquez does not suggest or disclose the existence of operator mutations which lead to an improvement in the thermostability of the binding affinity of a temperature sensitive λ repressor and thus does not cure the above discussed deficiencies in the other cited prior art. In view of the above discussion, applicants request that this rejection be withdrawn.

Claim 43 was rejected under 35 USC §103(a) as unpatentable over Eliason, in view of Pakula, Benson, Zacharias and Vasquez further in view of WO96/06164. WO96/06164 is cited for the disclosure of the use of a mutator bacterial strain. WO96/06164 does not suggest or disclose the existence of operator mutations which lead to an improvement in the thermostability of the binding affinity of a temperature sensitive λ repressor and thus does not cure the above discussed deficiencies in the other cited prior art. In view of the above discussion, applicants request that this rejection be withdrawn.

In the event this paper is not being timely filed, applicants respectfully petition for an appropriate extension of time. Any fees for such an extension together with any additional fees may be charged to Counsel's Deposit Account No. 01-2300.

Respectfully submitted,

ARENT FOX KINTNER PLOTKIN & KAHN, PLLC



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